## REMARKS

Upon entry of this amendment, Claims 5, 7-9, 26, 27, 29, 31, 37, 48-51, 56, 58, 69, 70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, 156, and 157 are pending in the present application. Among them, Claims 56, 110, 135, 137, 147, and 150 are directed to non-elected inventions or species, and are withdrawn from further consideration.

Applicants have amended Claim 5 by incorporating the subject matter of Claim 35 into Claim 5. As a result, Claim 35 is canceled.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

*Specification Objection*

The specification is objected to for containing hyperlinks and/or browser-executable codes. Applicants have amended the specification by destroying the hyperlinks and/or browser-executable codes (*e.g.*, removing "http://" or "www," reciting "dot," *etc.*). Reconsideration and withdrawal of the objections are respectfully requested.

*Sequence Compliance*

The Examiner requests Applicants to provide a sequence listing in compliance with 37 C.F.R. § 1.821(d), and to insert sequence identifiers in the claims / specification.

Applicants hereby submit a paper copy of the sequence listing together with the computer readable format (CRF), and respectfully request the Examiner to enter the sequence listing as part of the specification.

Applicants have also amended the specification and claims to insert the SEQ ID NOs. Reconsideration and withdrawal of the specification objections are respectfully requested.

*Claim Rejections under 35 U.S.C. § 102(b)*

Claims 5, 7-9, 26, 27, 31, 37, 69, 70, 72, 74, 78, 108, 117, 127-129, 150, 156, and 157 are

rejected under 35 U.S.C. § 102 (b), as allegedly being anticipated by Davis (or record).

The Examiner re-applied this previously withdrawn rejection, "because biological accretion moiety was considered as dead protein or dead cell, however, as applicant amended claim 1 [sic] by replacing biological accretion by insoluble protein-containing aggregate, the rejection is brought back."

While Applicants disagree with this broad interpretation, Applicants have amended independent Claim 5 to specifically recite that the "fusion protein" is a "contranslational fusion protein encoded by a recombinant nucleic acid" (emphasis added), thereby unambiguously distinguishing the presently claimed subject matter from those disclosed in Davis. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 (b) are respectfully requested.

Claims 5, 7-9, 26, 27, 37, 69, 70, 72, 74, 78, 108, 117, 127-129, 150, 156, and 157 are rejected under 35 U.S.C. § 102 (b), as allegedly being anticipated by Holvoet (or record).

The Examiner states that "[i]n the prior action of date 2/5/08, 35 U.S.C. 102(b) rejection as being anticipated by Holvoet et al. was withdrawn because biological accretion moiety was considered as dead protein or dead cell, however, as applicant amended claim 1 [sic] by replacing biological accretion by insoluble protein-containing aggregate, the rejection is brought back."

Applicants submit that the 35 U.S.C. § 102(b) rejection based on Holvoet was withdrawn because Holvoet fails to teach an adzyme that both binds to and cleaves the same substrate, not because of the nature of the substrate. As the Examiner admits, the construct in Holvoet relates to a fusion protein comprising a urokinase-type plasminogen activator (uPA) and a fibrin-specific antibody. The fusion protein binds the fibrin clot via its fibrin-specific antibody, but the uPA catalytic domain does not cleave the fibrin clot. Instead, it cleaves the soluble zymogen plasminogen in the circulating blood to yield an active Ser protease plasmin, which in turn dissolves the fibrin clot. In other words, Holvoet describes a fusion protein comprising an targeting domain (i.e., the fibrin-specific antibody) that does not bind the substrate (i.e., the plasminogen) which the catalytic domain (uPA) cleaves. In contrast, the claimed invention

requires the targeting domain to bind the same substrate which the catalytic domain cleaves.

Therefore, Holvoet cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 (b) are respectfully requested.

*Claim Rejections under 35 U.S.C. § 103(a)*

Claims 5, 7-9, 26, 27, 35, 37, 69, 70, 72, 74, 78, 108, 117, 127-129, 150, 156, and 157 are rejected under 35 U.S.C. § 103 (a), as allegedly being obvious over Davis (or record) in view of Bhatia (*Intl. J. Cancer* 2000, 85, 571-577).

Specifically, the Examiner states that Davis teaches a "fusion protein" wherein enzymes are chemically cross-linked to binding partners (*i.e.*, "chemically cross-linked fusion protein not a fusion protein made by cotranslation of respective genes"). The Examiner further states that protein conjugates can be made either by chemical cross-linking or by gene fusion, "but gene fusion methods have some particular advantages." The Examiner cited the last paragraph page 571, col. 1 in Bhatia to support this argument, and argues that one of skill in the art, in view of Davis and Bhatia, would have been "motivated to make the protein conjugate of Davis *et al.* by gene fusion methodology as taught be Bhatia *et al.*"

Applicants respectfully disagree. Applicants submit that it is improper to combine Davis with Bhatia, because doing so would require one of skill in the art to directly contradict the explicit teaching of Davis (to use chemical cross-linking) and use a method (the gene fusion method of Bhatia) that is specifically taught away by Davis.

Pursuant to MPEP 2143.01: "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A., 1959)."

Here, Davis explicitly teaches the use of chemical cross-linking for its various perceived advantages, which advantages are allegedly missing in cotranslational fusion proteins. In view of this specific teaching, one would not be *motivated* to ignore the chemical cross-linking method, and use the disfavored gene fusion methodology, despite the fact that the latter may

have some other advantages not sought after in Davis. In other words, one of skill in the art would not attempt to alter the principal of operation of Davis by modifying it with the Bhatia method. There is simply cannot be a "fusion protein of Davis *et al.* by the method Bhatia *et al.*" based on the disclosure in Davis and Bhatia.

Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Claims 29 and 31 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Davis (*supra*) in view of Bhatia *et al.* (*Supra*) and further in view of Guo (or record).

Guo allegedly teaches a fusion protein with a $(Gly_4Ser)_3$ linker. The Examiner argues that it would have been obvious for one of skill in the art to use the Guo linker in a "fusion protein as taught by David *et al.* by the method Bhatia *et al.*"

Applicants have argued above that Davis and Bhatia cannot be combined the way the Examiner suggested, because doing so would require one of skill in the art to change the principle of operation of the prior art invention being modified. Since Guo does not remedy this defect, the cited art still cannot be combined the way the Examiner suggests. Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

*Double Patenting Rejection*

The Office Action maintains the provisional obviousness-type double patenting rejection of Claims 5, 7-9, 26, 27, 29, 31, 35, 37, 52, 53, 58, 69, 70, 72, 74, 78, 108, 119, 127-129, and 131-134 over "Claims 1, 4, 5, 30-34, and 37-41 of co-pending Applications No. 10/792,498 and 10/650,591."

Applicants reiterate that, if conflicting claims are first allowed in these two co-pending U.S. Applications, and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

## CONCLUSION

Applicants submit that the application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P01-001**.

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Respectfully submitted,

By_____

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